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EXAMINER	
DUFFY, BRADLEY	
ART UNIT	**PAPER NUMBER**
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/729,441	SINGH ET AL.	
	Examiner	Art Unit	
	Brad Duffy	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *20,21,25,28 and 29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19,22-24,26,27 and 30-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/08/03,08/25/04, 08/03/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Exhibt A, B and C*.

DETAILED ACTION

1. The amendments filed August 03, 2005 and September 7, 2006 have been entered.

2. Claims 32-34 are newly added.

3. Claims 1-34 are pending.

4. Claims 20, 21, 25, 28 and 29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

5. Claims 1-19, 22-27 and 30-34 are under examination.

Election/Restrictions

6. Applicant's election without traverse of Group I, claims 1-18 and 23 in the reply filed on September 7, 2006, is acknowledged. Furthermore, applicant's election of species bortezomib (PS-341) is acknowledged. However, upon further consideration Group II will be rejoined and claims 19, 22, 24, 26, 27, 30, 31, and 34 will also be examined to the extent they read on a method of inhibiting the growth of cancer cells and the species requirement for Group II is withdrawn. Additionally, for the species election of Group I, gemcitabine is rejoined.

Information Disclosure Statement

7. The references cited in the information disclosure statements filed on May 12, 2005, February 3, 2006, and July 26, 2006, have been considered.

Priority

8. Applicant's claim under 35 USC §§ 119 and/or 120 for benefit of the earlier filing date of the 10/170,390, filed June 14, 2002, is acknowledged.

However, claims 1-19, 22-27 and 30-34 do not properly benefit under 35 U.S.C. §§ 119 and/or 120 by the earlier filing dates of the priority documents claimed, since those claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure.

To receive benefit of the earlier filing date under 35 USC §§ 119 and/or 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

In addition, claims 2, 17, 23, 30, and 32-34 do not properly benefit by the earlier filing because, although the document describes a composition comprising an antibody and a second agent, it does not describe such a composition comprising any of the agents of claim 2, nor does it describe such a composition in a kit, *per se*.

Accordingly, the effective filing date of the claims is deemed the filing date of the instant application, namely June 14, 2002.

Specification

9. The disclosure is objected to because of the following informalities:

a. The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

An example of such an improperly demarcated trademark appearing in the specification is Bexxar™ (see, e.g., page 11, paragraph 32).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

b. There are numerous typographical errors, occurring at least between pages 61 through 65, wherein question marks appear to be incorrectly included in sentences such as,

> "[167] The molecular model above, generated with the AbM software package, was analyzed to determine which EM164 surface residues were within 5? of a CDR."

and

> "A chimeric version of EM164 antibody with 92F? C mutation in heavy chain showed a slope of about 3 in similar binding competition with murine EM164 antibody, which indicated that the 92F? C mutant of EM164 had a 3-fold lower affinity than did murine EM164 antibody for binding to IGF-I receptor."

Applicant is requested to remove these question marks where they are inappropriate or provide clarification as to why they are appropriate.

c. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: The specification does not provide proper antecedent basis for the recitation of thalidomide, vincristince, interferon alpha-2a, carmustine, pamidronate, prednisone, erythropoietin and bisohosphonate as second agents.

d. The specification is objected to because of the incorporation by reference of second agents from DeVita el al (see paragraph 93 and 181). MPEP § 608.01(p) does

not provide for the incorporation by reference of essential material by reference to non-patent publications. "Essential material" is defined as "that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe the best mode (35 U.S.C. 112)". The second agents not disclosed in the specification are essential information because, for example, claim 2 presently recites, that second agents may be selected from: thalidome, carmustine, prednisone, pamidronate, erythropoitin and bisphosphonate and accordingly the disclosure is necessary to both describe and enable the claimed invention. Amending the claims to no longer claim these second agents would remedy this issue, or amending the specification to include the material incorporated by reference may remedy this issue provided no new matter is introduced. Applicant is cautioned that introduction of less then the entirety of the above reference into the specifation would be considered new matter. The amendment must be accompanied by an affidavit or declaration executed by Applicant, or a practitioner representing Applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

e. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction is required.

Claim Objections

10. Claims 4 and 5 objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Since, claim 1 is

not a process claim, the process limitations that are recited in claims 4 and 5, so not properly limit the composition of claim 1.

11. Claim 15 is objected to because the claim recites, "(a) a first therapeutic agent, wherein said first therapeutic agent is an antibody or fragment thereof comprising a light chain variable region having a sequence selected from the group consisting of:

DVVMTQTPLSLPVSLGDPASISCRSSQSIVHSNVNTYLEWYLQKPGQSPRLLIY KVSNRFSGVPDRFSGSGAGTDFTLRISRVEAEDLGIYYCFQGSHVPPTFGGGTKLEIK R (SEQ ID NO:9);

DVLMTQTPLSLPVSLGDPASISCRSSQSIVHSNVNTYLEWYLQKPGQSPKLLIYK VSNRFSGVPDRFSGSGAGTDFTLRISRVEAEDLGIYYCFQGSHVPPTFGGGTKLEIKR (SEQ ID NO:10);

DVLMTQTPLSLPVSLGDPASISCRSSQSIVHSNVNTYLEWYLQKPGQSPRLLIY KVSNRFSGVPDRFSGSGAGTDFTLRISRVEAEDLGIYYCFQGSHVPPTFGGGTKLEIK R (SEQ ID NO:11);

DVVMTQTPLSLPVSLGDPASISCRSSQSIVHSNVNTYLEWYLQKPGQSPKLLIY KVSNRFSGVPDRFSGSGAGTDFTLRISRVEAEDLGIYYCFQGSHVPPTFGGGTKLEIK R (SEQ ID NO:I2)", which is improper Markush-type claim language. See MPEP § 2173.05(h).

This issue can remedied by amending claim 15 to recite, for example, ""(a) a first therapeutic agent, wherein said first therapeutic agent is an antibody or fragment thereof comprising a light chain variable region having a sequence selected from the group consisting of:

DVVMTQTPLSLPVSLGDPASISCRSSQSIVHSNVNTYLEWYLQKPGQSPRLLIY KVSNRFSGVPDRFSGSGAGTDFTLRISRVEAEDLGIYYCFQGSHVPPTFGGGTKLEIK R (SEQ ID NO:9);

DVLMTQTPLSLPVSLGDPASISCRSSQSIVHSNVNTYLEWYLQKPGQSPKLLIYK VSNRFSGVPDRFSGSGAGTDFTLRISRVEAEDLGIYYCFQGSHVPPTFGGGTKLEIKR (SEQ ID NO:10);

DVLMTQTPLSLPVSLGDPASISCRSSQSIVHSNVNTYLEWYLQKPGQSPRLLIY KVSNRFSGVPDRFSGSGAGTDFTLRISRVEAEDLGIYYCFQGSHVPPTFGGGTKLEIK R (SEQ ID NO:11); and

DVVMTQTPLSLPVSLGDPASISCRSSQSIVHSNVNTYLEWYLQKPGQSPKLLIY KVSNRFSGVPDRFSGSGAGTDFTLRISRVEAEDLGIYYCFQGSHVPPTFGGGTKLEIK R (SEQ ID NO:12)" (underlining for emphasis).

c. Claims 22, 30, 31 and 34 are objected to for being drawn to a non-elected invention. Note: New claim 34 is alternatively directed to the subject matter of the non-elected invention of Group III.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claim 1-6, 8-14, 16-18, 19, 22, 30 and 32-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 1-6, 19, 22, and 32 are indefinite because claim 1 recites an antibody having at least one nucleotide mutation, deletion or insertion. Since antibodies are polypeptides, it is unclear how an antibody could have a nucleotide mutation, deletion or insertion. Accordingly, this claim is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(b) Claims 1-6, 19, 22, and 32 are indefinite because claim 1 recites, "an antibody, or epitope-binding fragment thereof, having the same amino acid sequence as the murine antibody EM164 produced by mouse hybridoma EM164." Since such murine antibodies consist of a 2 heavy and 2 light chain polypeptides, each of which comprise a separate amino acid sequence, it is unclear to which sequence the claims are directed.

Furthermore, how can an antibody fragment have the same sequence as a whole antibody?

(c) Claims 2, 17, and 30 contain the trademark/trade names HERCEPTIN, AVASTIN, RITUXAN, ZEVALIN, VELCADE, TARCEVA, CETUXIMAB and ABX-EBF. Claims 32-34 contain the trademark/trade name VELCADE. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe second agents and, accordingly, the identification/description is indefinite.

(d) Claims 8-14 and 16 are indefinite in the recitation of "represented by..." in claims 8-14 and 16 because it is unclear what is contemplated by the phrase. The phrase "represented by" renders the claims indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. For example, must the antibody, comprise or consist of the recited SEQ ID Nos, or may the antibody be a functional equivalent of an antibody with the recited SEQ ID Nos? See MPEP § 2173.05(d). Amending the claims to recite "comprising the amino acid sequence of SEQ ID NO:X", for example, would overcome this rejection.

(e) Claims 4 and 5 are indefinite for reciting a process limitation in a product claim, in an attempt to further limit the composition of claim 1. Since, claim 1 is not a process claim, it is unclear how the process limitation that is recited further limits the composition. Accordingly, these claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(f) Claim 32 recites the limitation "the method of claim 1". However, claim 1 is drawn to a composition; and as such, claim 32 finds no antecedent basis for this limitation in the preceding claim.

Accordingly, these claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim Rejections - 35 USC § 112

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 1-19, 22, 32 and 33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a WRITTEN DESCRIPTION rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

Claims 1-6, 19, 22 and 32 are directed to functional equivalents or variants of antibodies, having at least one amino acid mutation, deletion or insertion compared to murine antibody EM164 (due to the indefiniteness of referring to an antibody with a nucleotide mutation, the antibodies are interpreted as having amino acid changes) that are structurally disparate.

While the specification teaches functional equivalents or variants of antibodies can be polypeptides with amino acids substantially the same as the antibodies of the invention, antibody fragments, humanized variants, or variants where the amino acid

sequence of the primary antibody was changed, the specification does not describe the genus of antibodies encompassed by functional equivalents or variants of antibodies, having at least one amino acid mutation, deletion or insertion compared to murine antibody EM164 as it does not describe which specific amino acids in the variable heavy and light chain regions are important for binding to insulin-like growth factor-I receptor.

As such, while the specification describes antibodies that specifically bind insulin-like growth factor-I receptor or epitope-binding antibody fragments of insulin-like growth factor-I receptor, (e.g., EM164), none are representative of the genus, as a whole, since there is no disclosure of a correlation between any one particularly identifying (i.e., substantial) structural feature, which is shared by these antibodies and other functional equivalents or variants of antibodies to which the claims are directed, and any one functional feature also shared by at least most of the genus.

Consequently, the skilled artisan could not immediately envision, recognize or distinguish at least most of the members of the genus of functional equivalents or variants of antibodies to which the claims are directed; and therefore the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed

Claims 7-18 and 33 are directed to antibodies or fragments thereof, which do not necessarily bind to any one antigen; thus, although the claimed antibodies comprise at least one of the recited complementarity-determining region sequences (CDRs) or are represented by the said CDRs, the antibodies are otherwise structurally and functionally disparate. Claims 9-18 are further drawn to an antibody or antibody fragment that has a heavy or light chain that is 90-95% identical to an amino acid sequence represented by one of SEQ ID Nos:7-13.

While the specification teaches antibodies or fragments thereof that bind insulin-like growth factor-I receptor, no other antigen has been described with particularity; yet, the claims encompass antibodies having no particular binding specificity or function, such as antibodies that bind an antigen other than insulin-like growth factor-I receptor.

Furthermore, while the specification teaches antibodies or fragments thereof that bind insulin-like growth factor-I receptor, which comprise each of the six CDRs of monoclonal antibody EM164, it fails to describe with particularity any such antibody lacking one or more of these CDRs but having or retaining this binding specificity, nor does it disclose any other heavy or light chain variable regions that are 90-95% identical to the heavy and light chains of one of SEQ ID Nos:7-13 that retain this binding specificity.

As such, while the specification describes monoclonal antibody EM164 and humanized or resurfaced antibodies that have all six of the recited CDRs of EM164, it is not representative of the genus, as a whole, since there is no disclosure of a correlation between any one particularly identifying (i.e., substantial) structural feature, which is shared by monoclonal antibody EM164 and other antibodies to which the claims are directed, and any one functional feature also shared by at least most of the genus.

Consequently, the skilled artisan could not immediately envision, recognize or distinguish at least most of the members of the genus of antibodies and fragments thereof to which the claims are directed; and therefore the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description" Requirement (66 FR 1099-1111, January 5, 2001; hereafter "Guidelines") states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). "Guidelines" further states, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus.

Because the claims encompass a genus of structurally and/or functionally variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant had possession of the claimed invention at the time the application was filed.

16. Claims 7, 17, 18 and 33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

The response filed 08/03/2005 has introduced NEW MATTER into the claims. Claims 7, 17, 18 and 33 recite a newly added limitation, wherein "when SEQ ID NO:5 is selected said antibody or antibody fragment specifically binds to insulin-like growth factor-I receptor." While the response points out where support for the newly added second agents could be found in the originally filed disclosure, it was not found persuasive.

Applicant submits that the support for the amendment may be found throughout the specification, such as in paragraph 62 that states,

"[0062] The present inventors have discovered and improved novel antibodies that specifically bind to the human insulin-like growth factor-I receptor (IGF-R) on the cell surface. The antibodies and fragments have the unique ability to inhibit the cellular functions of the receptor without the capacity to activate the receptor themselves. Thus, while previously known antibodies that specifically bind and inhibit IGF-IR also activate the receptor even in the absence of IGF-IR ligands, the antibodies or fragments of the present invention antagonize IGF-IR but are substantially devoid of agonist activity.

Furthermore, the antibodies and antibody fragments of the present invention inhibit the growth of human tumor cells such as MCF-7 cells in the presence of serum by greater than 80%, which is a higher degree of inhibition than is obtained using previously known anti-IGF-IR antibodies."

However, while this provides support for antibodies that bind insulin-like growth factor-I receptor, it does not provide support for an antibody specifically binding insulin-like growth factor-I receptor when SEQ ID NO: 5 is selected. Additionally, such support could not be found after looking through the specification. If such support is found elsewhere in the specification, applicant is requested to specifically point where the support occurs in the specification.

Thus, the specification lacks information to lead one of skill in the art to understand that the applicant had possession of the broadly claimed invention at the time the instant application was filed. Therefore, one of skill in the art would not understand that the applicant had possession of the claimed invention at the time the instant application was filed.

Instant claims 7, 17, 18 and 33 now recite limitations, which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in claims 7, 17, 18 and 33, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C 112. Applicant is required to provide sufficient written support for the limitations recited in present claims 7, 17, 18 and 33 in the specification or claims, provided no new matter is introduced, or remove these limitations from the claims in response to this Office Action.

17. Claims 2, 17, 30, and 32-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

The response filed 09/07/2006 has introduced NEW MATTER into the claims. Claims 2, 17, 30, and 32-34 recite newly added second agents thalidomide, carmustine, pamidronate, prednisone, erythropoietin, bisohosphonate, interferon alpha-2a and vincristine. While the response points out where support for the newly added second agents could be found in the originally filed disclosure, it was not found persuasive.

Applicant submits that the support for the second agents thalidomide, carmustine, pamidronate, prednisone, erythropoietin and bisohosphonate is found in DeVita et al that is cited in paragraph 93 and is incorporated by reference. However, the agents in question do not appear in the large list of agents that appear in paragraph 93, as filed, and applicant did not *particularly* point to disclosures in DeVita et al. describing thalidomide, carmustine, pamidronate, prednisone, erythropoietin and bisohosphonate, per se.

Therefore, contrary to Applicant's contention, this disclosure does not appear to provide support for the added material because it does not *particularly* identify the added material.

According to M.P.E.P. 608.01(p):

> Mere reference to another application, patent, or publication is not an incorporation of anything therein into the application containing such reference for the purpose of the disclosure required by 35 U.S.C. 112, first paragraph. *In re de Seversky*, 474 F.2d 671, 177 USPQ 144 (CCPA 1973).

With regard to incorporation by reference, the Federal Circuit in deciding *Advanced Display Systems Inc. v. Kent State University,* 54 USPQ2d 1673 (CA FC), has further opined:

> Incorporation by reference provides a method for integrating material from various documents into a host document--a patent or printed publication in an anticipation determination--by citing such material in a manner that makes clear that the material is effectively part of the host document as if it were explicitly contained therein. *See General Elec. Co. v. Brenner*, 407 F.2d 1258, 1261-62, 159 USPQ 335, 337 (D.C. Cir. 1968); *In re Lund*, 376 F.2d 982, 989, 153 USPQ 625, 631 (CCPA 1967). To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents. *See In re Seversky*, 474 F.2d 671, 674, 177 USPQ 144, 146 (CCPA 1973) (providing that incorporation by reference requires a statement

> "clearly identifying the subject matter which is incorporated and where it is to be found"); *In re Saunders*, 444 F.2d 599, 602-03, 170 USPQ 213, 216-17 (CCPA 1971) (reasoning that a rejection for anticipation is appropriate only if one reference "expressly incorporates a particular part" of another reference); *National Latex Prods. Co. v. Sun Rubber Co.*, 274 F.2d 224, 230, 123 USPQ 279, 283 (6th Cir. 1959) (requiring a specific reference to material in an earlier application in order have that material considered part of a later application); *cf. Lund*, 376 F.2d at 989, 153 USPQ at 631 (holding that a one sentence reference to an abandoned application is not sufficient to incorporate material from the abandoned application into a new application). Whether and to what extent material has been incorporated by reference into a host document is a question of law. *See Quaker City Gear Works, Inc. v. Skil Corp.*, 747 F.2d 1446, 1453-54, 223 USPQ 1161, 1166 (Fed. Cir. 1984) (reasoning that whether a document is incorporated by reference into a patent presents a question of law when determining enablement). *Id.* at 1679-1680.
>
> [Thus] the standard of one reasonably skilled in the art should be used to determine whether the host document describes the material to be incorporated by reference with sufficient particularity. *Id.* at 1680.

Applicant submits that the support for the second therapeutic agent interferon alpha-2a may be found in paragraph 92 that states,

> "[0092] Cancer therapeutic agents are those agents that seek to kill or limit the growth of cancer cells while doing minimal damage to the host. Thus, such agents may exploit any difference in cancer cell properties (e.g. metabolism, vascularization or cell-surface antigen presentation) from healthy host cells. Differences in tumor morphology are potential sites for intervention: for example, the second therapeutic can be an antibody such as an anti-VEGF antibody that is useful in retarding the vascularization of the interior of a solid tumor, thereby slowing its growth rate. Other therapeutic agents include, but are not limited to, adjuncts such as granisetron HCl, androgen inhibitors such as leuprolide acetate, antibiotics such as doxorubicin, antiestrogens such as tamoxifen, antimetabolites such as interferon alpha-2a, cytotoxic agents such as taxol, enzyme inhibitors such as ras farnesyl-transferase inhibitor, immunomodulators such as aldesleukin, and nitrogen mustard derivatives such as melphalan HCl, and the like."

However, this is not found persuasive, since the above paragraph only provides support for interferon alpha-2a as a cancer therapeutic agent as the entire paragraph is devoted to describing cancer therapeutic agents.

Applicant submits that the support for the second therapeutic agent vincrisitne may be found in paragraph 83 that states,

"[0083] Cytotoxic drugs such as methotrexate, daunorubicin, doxorubicin, vincristine, vinblastine, melphalan; mitomycin C, chlorambucil, and calicheamicin are also suitable for the preparation of conjugates of the present invention, and the drug molecules can also be linked to the antibody molecules through an intermediary carrier molecule such as serum albumin."

However, this is not found persuasive, since the above paragraph only provides support for vincristine as a cytotoxic agent that is conjugated to the present invention.

Thus, the specification lacks information to lead one of skill in the art to understand that the applicant had possession of the broadly claimed invention at the time the instant application was filed. Therefore, one of skill in the art would not understand that the applicant had possession of the claimed invention at the time the instant application was filed.

Instant claims 2, 17, 30, and 32-34 now recite limitations, which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in claims 2, 17, 30, and 32-34, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C 112. Applicant is required to provide sufficient written support for the limitations recited in present claims 2, 17, 30, and 32-34 in the specification or claims, provided no new matter is introduced, or remove these limitations from the claims in response to this Office Action.

18. Claims 1-6, 19, 22-24, 26, 27, 30-32 and 34 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

It is unclear if a cell line, which produces an antibody having the exact chemical identity of antibody EM164 is known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different VH chains (about 50% homologous) can combine with the same VK chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different VH sequences combine with different VK sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY page 242 (William E. Paul, M.D. ed., 3d ed; 1993, IDS filed August 03, 2005)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species antibody EM164.

The specification lacks complete deposit information for the deposit of antibody EM164. It is unclear whether antibodies possessing the identical properties of antibody EM164 are known and publicly available or can be reproducibly isolated from nature without undue experimentation.

Because one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed in the absence of the availability of the claimed antibody EM164, a suitable deposit is required for patent purposes, evidence of public availability of the claimed antibody or evidence of the reproducibility without undue experimentation of the claimed antibody, is required.

Applicant's referral to the deposit of the hybridoma producing the EM164 antibody on page 69 of the specification is an insufficient assurance that the required deposit has been made and all the conditions of 37 CFR 1.801-1.809 met.

As the deposit was made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit of the hybridoma producing monoclonal antibody EM164 has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that the deposit will be replaced if viable samples cannot be dispensed by the depository, that all restrictions upon public access to the

deposited material will be irrevocably removed upon the grant of a patent on this application and access to the deposit will be available during pendency of the patent application making reference to the deposit to one determined by the Commissioner to be entitled thereto under 37 CFR 1.14 and 35 U.S.C. 122 is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves these specific matters to the discretion of each State.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

19. Claims 1-19, 22-27 and 30-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making and using** a composition comprising an antibody or antibody fragment that specifically binds to an insulin-like growth factor-I receptor (IGF-I-R), wherein said antibody or antibody fragment comprises the amino acid sequence of 6 sequential CDRs, wherein the CDRs are SEQ ID Nos:1-6 or antibodies taught in the prior art that specifically bind IGF-I-R, **does not reasonably provide enablement for making and using** a composition comprising (i) functional equivalents or variants of antibodies (claim 1) or (ii) an antibody or antibody fragment comprising an amino acid sequence from at least one CDR selected from SEQ ID Nos:1-6, wherein the antibody or antibody fragment does not bind IGF-I-R (claim 7) or (iii) an antibody or antibody fragment comprising an amino acid sequence represented by (SEQ ID Nos:1-6) (claim 8) or (iv) an antibody or antibody fragment comprising an amino acid sequence of a heavy or light chain that is 90-95% identical to one of SEQ ID Nos:7-13, wherein the antibody or antibody fragment does not bind IGF-I-R (claims 9-10, 12-13 and 15-18) or (v) an antibody or antibody fragment comprising an amino acid sequence of a heavy or light chain represented by SEQ ID No:7 or 8, wherein the antibody or antibody fragment does not bind IGF-I-R, wherein the antibody or antibody fragment does not bind IGF-I-R (claims 11 and 14, respectively) or (vi) an antibody or antibody fragment that specifically binds IGF-I-R comprising at least one CDR selected from SEQ ID Nos:1-6 or comprising a heavy or light chain that is 90-95%

identical to one of SEQ ID NO:7-13, respectively. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

The claims are drawn to functional equivalents or variants of antibodies or antibody or antibody fragment comprising at least one CDR selected from SEQ ID Nos:1-6 or comprising all six CDRs (SEQ ID Nos:1-6) or comprising a heavy or light chain that is 90-95% identical to one of SEQ ID Nos:7-13, respectively, wherein the

antibody or antibody fragment does not bind IGF-I-R; and an antibody or antibody fragment that specifically binds IGF-I-R comprising at least one CDR selected from SEQ ID Nos:1-6 or comprising a heavy or light chain that is 90-95% identical to one of SEQ ID Nos:7-13, respectively. The specification discloses only antibodies that have 6 CDRs that specifically bind IGF-I-R and comprise all 6 CDRs of SEQ ID Nos:1-6 (see Examples).

The specification does not enable functional equivalents or variants of antibodies or antibodies comprising at least one CDR selected from SEQ ID Nos:1-6 or comprising all six CDRs (SEQ ID Nos:1-6) or comprising a heavy or light chain that is 90-95% identical to one of SEQ ID Nos:7-13, respectively, wherein the antibody or antibody fragment does not bind IGF-I-R; or antibodies that specifically bind IGF-I-R comprising at least one CDR selected from SEQ ID Nos1-6 or comprising a heavy or light chain that is 90-95% identical to one of SEQ ID Nos:7-13, respectively.

The claims encompass functional equivalents or variants of antibodies or antibody or antibody fragment comprising only one CDR selected from SEQ ID Nos:1-6 or the antibody comprises a heavy chain having an amino acid sequence that is 90-95% identical to SEQ ID NO:7 or 13, or the antibody comprises a light chain having an amino acid sequence that is 90-95% identical to one of SEQ ID NO:8-12 and the antibody does not bind antigen or binds IGF-I-R. It is well established in the art that the formation of an intact antigen-binding site of all antibodies requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions,

particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc. Natl. Acad. Sci. USA 1982 Vol. 79: page 1979, IDS filed August 03, 2005). Rudikoff et al teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that antibodies that do not contain all of SEQ ID Nos:1-6, or antibodies comprising a heavy chain or a light chain having an amino acid sequence that is 90-95% identical to SEQ ID Nos:7 or 8, respectively, as defined by the claims, have the required binding function. For example, Watkins et al (US 2003/0099655 A1, 5/29/2003, IDS filed August 03, 2005) teach an antibody comprising a light chain (Vk domain of HUI77) that is 95% identical to SEQ ID NO:8 and the antibody binds collagen. The specification provides insufficient evidence or nexus that would lead the skilled artisan to predict the ability of producing antibodies comprising fewer than all six CDRs (SEQ ID Nos:1-6) and bind IGF-I-R or an antibody comprising a heavy chain having an amino acid sequence that is 90-95% identical to SEQ ID NO:7 or 13 and binds IGF-I-R or an antibody comprising a light chain having an amino acid sequence that is 90-95% identical to one of SEQ ID NO:8-12 and binds IGF-I-R. Although the specification at pages 17-18 states that diverse antibody and antibody fragments, as well as antibody mimics may be readily produced by mutation, deletion and/or insertion within the variable and constant regions and functional equivalents include polypeptides with amino acid sequences substantially the same as the amino acid sequence of the variable or hypervariable regions of the antibodies of the invention, the specification does not provide sufficient guidance or direction as to the general tolerance to modification and extent of such tolerance in the variable and constant regions; the specific positions of the variable and constant regions which can be predictably modified and which regions are critical for maintaining antigen specificity and affinity for IGF-I-R and functions as an IGF-I-R antagonist that is substantially devoid of agonist activity.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as

filed, is not deemed sufficient to have enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Claim Rejections - 35 USC § 102

20. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

21. Claims 1, 4-6, 8-14, 16, 19 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Zia et al (Journal of Cellular Biochemistry Supplement 24:269-275, 1996, IDS filed August 03, 2005).

The claims are interpreted as being drawn to a composition or pharmaceutical composition comprising a functional equivalent or variant of monoclonal antibody EM164 that specifically binds to insulin-like growth factor-I receptor or an antibody represented by SEQ ID Nos: 1-13 and a second agent. The claims are further drawn to a method of inhibiting the growth of cancer cells with said composition, wherein said cancer cell is lung cancer. The examiner is interpreting the word therapeutic in these claims as an intended use of the agent and therefore is not considering it a limitation of the second agent, as it does not materially and/or structurally define the agent.

Zia et al teach antibody IR-3 that specifically binds to insulin-like growth factor-I receptor (see whole document, e.g., page 270). Zia et al also teach conjugating αIR-3 to ^{125}I, wherein ^{125}I is considered a second agent (e.g., abstract). Finally, Zia et al teach ^{125}I-αIR-3 in a pharmaceutical composition for injection into mice and that this composition inhibits the growth of lung cancer cells (e.g., page 273). Thus, Zia et al anticipate these claims.

22. Claims 7-11, 16, 19 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Kettleborough et al (USP (e.g., page 273), December 1, 1998).

The claims are interpreted as being drawn to a composition of an antibody having an amino acid sequence from one complementarity-determining region from SEQ ID Nos:1-6, an amino acid sequence from SEQ ID Nos: 7 or 13 or having amino acid sequences represented by SEQ ID Nos: 1-7 or 13 and a second agent. The claims are further drawn to a method of inhibiting the growth of melanoma cancer cells.

Kettleborough et al teach an antibody that comprises a CDR that is identical to SEQ ID No:1 (see exhibit A attached to the end of this office action). Furthermore, Kettleborough et al teach this antibody in a composition with antibiotics or cytokines and conjugated to a cytotoxic agent for the treatment of melanoma cancer cells (see entire document, e.g., column 12, lines 1-12). Thus, Kettleborough et al anticipate these claims.

23. Claims 7-8 and 12-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Do Couto et al (USP 6,309,636, October 30, 2001).

The claims are interpreted as being drawn to a composition of an antibody having an amino acid sequence from one complementarity-determining region from SEQ ID Nos:1-6, an amino acid sequence from SEQ ID Nos: 8-12 or having amino acid sequences represented by SEQ ID Nos: 1-6 or 8-12 and a second agent. The claims are further drawn to a method of inhibiting the growth of carcinoma cancer cells.

Do Couto et al teach an antibody with a CDR that is identical to SEQ ID No:6 (see exhibit B attached to the end of this office action). Furthermore, Do Couto et al teach this antibody in a composition with a radioactive isotope for the treatment of carcinoma cells (see entire document, e.g., column 2, line 60-67). Thus, Do Couto et al anticipate these claims.

24. Claims 8-17, 19 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Tan et al (Cancer Research 62:1083-1086, February 15, 2002) as evidenced by Queen et al (USP 5,530,101, June 25, 1996, IDS filed August 03, 2005).

The claims are interpreted as being drawn to a composition of an antibody having an amino acid sequence of at least two consecutive amino acids in length from complementarity-determining regions represented by SEQ ID Nos:1-6 or an amino acid sequence at least two amino acids in length represented by SEQ ID Nos: 7-13 and a second agent. The claims are further drawn to the second agent being bortezomib (PS-341) and a method of inhibiting the growth of cancer cells with such a composition.

Tan et al teach the antibody, humanized anti-Tac, in a composition with PS-341 (see entire document, e.g., abstract) (PS-341 is a designation for bortezomib, see Exhibit C attached to end of office action). As evidenced by Queen et al, humanized anti-Tac has an amino acid sequence from complementarity-determining regions represented by SEQ ID Nos:1-6 and an amino acid sequence represented by SEQ ID Nos: 7-13. (See SEQ ID No:5 or SEQ ID No:7 of patent '101). For example, SEQ ID No:5 of patent '101 is the amino acid sequence of the variable heavy chain region of humanized anti-Tac and has the sequence "SY" in it, which corresponds to the sequence "SY" in SEQ ID NO:1, SEQ ID NO:7 and SEQ ID NO:13 of the present application and SEQ ID No:7 of patent '101 is the amino acid sequence of the variable light chain region of humanized anti-Tac and has the sequence SS in it, which corresponds to the sequence SS in SEQ ID NO:4, and SEQ ID NOs:8-12 of the present application. Furthermore, Tan et al teach that the combination of PS-341 and anti-Tac inhibit the growth of certain cancer cells (e.g., Figure 3). Thus, Tan et al anticipate these claims.

25. Claim 1-18, 19, 22-24, 26, 27, 30, and 31 are rejected under 35 U.S.C. 102(a) as being anticipated by Maloney et al (Cancer Research 63:5073-5083, August 15, 2003, IDS filed August 25, 2004).

Claim 1-18, 19, 22, 24, 26, 27, 30, and 31 are interpreted as being drawn to a composition of the murine antibody EM164 that has an amino acid sequence from one complementarity-determining region from SEQ ID Nos:1-6 or an amino acid sequence from SEQ ID Nos: 7 or 13 and a second agent. The claims are further drawn to the second agent being gemcitabine and a method of inhibiting the growth of cancer cells by contacting the cells with an antibody EM164 either concurrently, or sequentially.

Claim 23 is drawn to a kit comprising an antibody that binds insulin-like growth factor-I receptor; although the claim recites the kit comprises "a second therapeutic agent", because the specification does not expressly define this term, it is broadly but reasonably interpreted to encompass virtually any other component (e.g., a buffer). As explained above, the recitation "therapeutic" is merely interpreted as an intended use of the agent; the recitation does not materially and/or structurally define the agent.

Maloney et al teach the murine antibody EM164 in a composition with gemcitabine and that the composition inhibits the growth of certain cancer cells and that the agents can contact the cells concurrently, or sequentially (see entire document, e.g., abstract and figure 7).

Furthermore, Maloney et al teach that other anti-IGF-IR antibodies are commercially available (e.g., page 5074, left column, Materials and Methods) and thus are sold in a "kit" (e.g., a container, a package, a vial, a box, etc.). Thus, absent a showing of any difference, the commercially available antibody is deemed the same as the claimed kit comprising the antibody.

Thus, Maloney et al anticipate these claims.

26. Claims 1, 4-6, 19, and 22 are rejected under 35 U.S.C. 102(b) as being anticipated Rohlik et al (Biochemical and Biophysical Research Communications 149:276-281, November 30, 1987).

The claims are interpreted as being drawn to a composition or pharmaceutical composition comprising a functional equivalent of monoclonal antibody EM164 that specifically binds to insulin-like growth factor-I receptor and a second agent. Finally the

claims are limited to a method of inhibiting the growth of cancer cells using the above composition.

Rohlik et al teach the antibody, alpha IR-3 that specifically binds to the insulin-like growth factor I receptor and is being considered a functional equivalent of murine antibody EM164 since it has the same binding specificity as EM164 (see entire document, e.g., page 276, first paragraph). Furthermore, Rohlik et al teach αIR-3 in a composition with ^{125}I-insulin-like growth factor I and that such a composition inhibits the growth of the breast cancer cell line, MCF-7 (e.g., figure 1 and 2). Thus, Rohlik et al anticipate these claims.

Claim Rejections - 35 USC § 103

27. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

28. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

29. Claims 1-2 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rohlik et al (Biochemical and Biophysical Research Communications 149:276-281, November 30, 1987), in view of Teicher et al (Clinical Cancer Research 5:2638-2645, September 1999).

The claims are interpreted as being drawn to a composition or pharmaceutical composition comprising a functional equivalent of monoclonal antibody EM164 that specifically binds to insulin-like growth factor-I receptor and a second agent, wherein the second agent is boretozomib (PS-341). Finally the claims are limited to a method of inhibiting the growth of cancer cells using the above composition.

Rohlik et al teach the antibody, alpha IR-3 that specifically binds to the insulin-like growth factor I receptor and is being considered a functional equivalent of murine antibody EM164 since it has the same binding specificity as EM164 (see entire document, e.g., page 276, first paragraph). Furthermore, Rohlik et al teach that αIR-3 inhibits the growth of the breast cancer cell line, MCF-7 (e.g., figure 1). Rohlik et al do not teach αIR-3 in a composition with boretozomib (PS-341). This deficiency is made up for in the teachings of Teicher et al.

Teicher et al teach that the proteasome inhibitor PS-341 (PS-341 is a lab designation for bortezomib) is a cytotoxic agent to MCF-7 cells and therefore inhibits their growth and/or causes their death (see entire document, e.g., page 2640 second column and figure 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was make to make a composition of αIR-3 and PS-341 and use it in basic research to inhibit the growth of MCF-7 cells.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention to make a composition of the αIR-3 antibody of Rohlik and the PS-341 agent of Teicher and use it in research to inhibit the growth of MCF-7 cells as both were known to be useful for the same purpose, i.e. inhibiting the growth of MCF-7 cells, so it would be *prima facie* obvious to combine two products that are useful for the same purpose to form a composition which is to be used for the very same purpose. See In re Kerhoven, 626 F.2d 848, 850, 205 USPQ 1069, 1072, (CCPA 1980). Thus, there would be an advantage and a reasonable expectation of success in making a composition of αIR-3 and PS-341 and use it in research to inhibit the growth of MCF-7 cells, in view of Rohlik et al and Teicher et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Double Patenting

30. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory

double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

31. Claims 1-18, 23 and 32-33 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-27 of copending Application No. 10/170,390 in view of Teicher et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application and the instant application are claiming common subject matter.

The instant claims are described supra.

Claims 1-27 of copending Application No. 10/170,390 encompass the scope of the instant claims 1-18, 23 and 32-33 because they are drawn to an antibody or fragment thereof and pharmaceutical compositions (comprises a pharmaceutically acceptable carrier) comprising an antibody or fragment thereof that specifically binds to an insulin-like growth factor-I receptor (IGF-I-R) or human IGF-I-R and an antibody or antibody fragment comprising at least one CDR selected from SEQ ID Nos:1-6 or comprising all six CDRs (SEQ ID Nos:1-6) or comprising a heavy or light chain that is 90-100% identical to one of SEQ ID Nos:7-13, respectively and an antibody or antibody fragment that specifically binds IGF-I-R comprising at least one CDR selected from SEQ ID Nos:1-6 or comprising a heavy or light chain that is 90-100% identical to SEQ ID NO:7 or 8, respectively, and an antibody or fragment thereof comprising a light chain variable region selected from SEQ ID Nos:9-12 or comprises the heavy chain variable region of SEQ ID NO:13 and the antibody or fragment thereof that binds IGF-I-R is linked to a cytotoxic agent. Further, the claims are drawn to antibody EM164 that is humanized or resurfaced. The claims in copending Application No. 10/170,390 do not

teach that the second agent is bortezomib (PS-341). This deficiency is made up for in the teachings of Teicher et al.

Teicher et al are described supra.

The claims in the instant application are obvious variants of claims 1-27 of copending Application No. 10/170,390 because it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to make a composition of an antibody or antibody fragment that specifically binds insulin-like growth factor receptor and PS-341 and use it to inhibit the growth of MCF-7 cells.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention to make a composition of antibody or antibody fragment that specifically binds insulin-like growth factor receptor and the PS-341 agent of Teicher and use it to inhibit the growth of MCF-7 cells as both are useful for the same purpose (see figure 8 of the drawings where EM164 is shown to inhibit the growth of MCF-7 cells), i.e. inhibiting the growth of MCF-7 cells.

Thus, the claims of the instant application and claims 1-27 of copending Application No. 10/170,390 are not patentably distinct one from the other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

32. Claims 19, 22, 24, 26, 27, 30, 31 and 34 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claim 30 of copending Application No. 10/170,390 in view of Teicher et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application and the instant application are claiming common subject matter.

The instant claims are described supra.

Claim 30 of copending Application No. 10/170,390 encompasses the scope of the instant claims 19, 22, 24, 26, 27, 30, 31 and 34 because it is method of inhibiting the growth of cancer cells, comprising contacting said cells with an antibody or fragment thereof that specifically binds to an insulin-like growth factor-I receptor (IGF-I-R). The

claims in copending Application No. 10/170,390 do not teach a method wherein a second agent is included or that the second agent is bortezomib (PS-341). This deficiency is made up for in the teachings of Teicher et al.

Teicher et al are described supra.

The claims in the instant application are obvious variants of claim 30 of copending Application No. 10/170,390 because it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to inhibit the growth of MCF-7 cancer cells with a composition comprising an antibody or antibody fragment that specifically binds to insulin-like growth factor-I receptor.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention to inhibit the growth of MCF-7 cancer cells with a composition comprising an antibody or antibody fragment that specifically binds to insulin-like growth factor receptor because both components of the composition are useful for the same purpose (see figure 8 of the drawings where the insulin-like growth factor-I receptor antibody, EM164 is shown to inhibit the growth of MCF-7 cells), i.e. inhibiting the growth of MCF-7 cells.

Thus, the claims of the instant application and claim 30 of copending Application No. 10/170,390 are not patentably distinct one from the other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

33. No claims are allowed.

34. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The examiner can normally be reached on Monday through Friday 7:00 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
Brad Duffy
571-272-9935

STEPHEN L. RAWLINGS, PH.D.
PRIMARY EXAMINER

Exhibit A

RESULT 19
US-08-553-497A-8
; Sequence 8, Application US/08553497A
; Patent No. 5844093
; GENERAL INFORMATION:
; APPLICANT: KETTLEBOROUGH, C. A.
; APPLICANT: BENDIG, MARY M.
; APPLICANT: ANSELL, KEITH H.
; APPLICANT: GUSSOW, DETLEF
; APPLICANT: ADAN, JAUME
; APPLICANT: MITJANS, FRANSESC
; APPLICANT: ROSELL, ELISABET
; APPLICANT: BLASCO, FRANCESC
; APPLICANT: PIULATS, JAUME
; TITLE OF INVENTION: ANTI-EGFR SINGLE-CHAIN FVS AND ANTI-EGFR
; TITLE OF INVENTION: ANTIBODIES
; NUMBER OF SEQUENCES: 30
; CORRESPONDENCE ADDRESS:
; ADDRESSEE: MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
; STREET: 2200 CLARENDON BLVD. SUITE 1400
; CITY: ARLINGTON
; STATE: VA
; COUNTRY: US
; ZIP: 22201
; COMPUTER READABLE FORM:
; MEDIUM TYPE: Floppy disk
; COMPUTER: IBM PC compatible
; OPERATING SYSTEM: PC-DOS/MS-DOS
; SOFTWARE: PatentIn Release #1.0, Version #1.30
; CURRENT APPLICATION DATA:
; APPLICATION NUMBER: US/08/553,497A
; FILING DATE: 17-NOV-1995
; CLASSIFICATION: 530
; PRIOR APPLICATION DATA:
; APPLICATION NUMBER: WO PCT/EP95/00978
; FILING DATE: 16-MAR-1995
; PRIOR APPLICATION DATA:
; APPLICATION NUMBER: EP 94104160.0
; FILING DATE: 17-MAR-1994
; PRIOR APPLICATION DATA:
; APPLICATION NUMBER: EP 94118970.6
; FILING DATE: 02-DEC-1994
; ATTORNEY/AGENT INFORMATION:
; NAME: HAMLET-KING, DIANA
; REGISTRATION NUMBER: 33,302
; REFERENCE/DOCKET NUMBER: MERCK 1726
; TELECOMMUNICATION INFORMATION:
; TELEPHONE: 703-243-6333
; TELEFAX: 703-243-6410
; INFORMATION FOR SEQ ID NO: 8:
; SEQUENCE CHARACTERISTICS:
; LENGTH: 119 amino acids
; TYPE: amino acid
; TOPOLOGY: linear
; MOLECULE TYPE: protein
US-08-553-497A-8

Query Match 100.0%; Score 35; DB 1; Length 119;
Best Local Similarity 100.0%; Pred. No. 43;
Matches 5; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

```
Qy          1 SYWMH 5
              |||||
Db         31 SYWMH 35
```

Exhibit B

RESULT 1
US-08-525-539A-17
; Sequence 17, Application US/08525539A
; Patent No. 6309636
; GENERAL INFORMATION:
; APPLICANT: DO COUTO, FERNANDO J.R.
; APPLICANT: CERIANI, ROBERTO L.
; APPLICANT: PETERSON, JERRY A.
; TITLE OF INVENTION: RECOMBINANT PEPTIDES DERIVED FROM THE
; TITLE OF INVENTION: Mc3 ANTI-BA46 ANTIBODY, METHODS OF USE THEREOF, AND
; TITLE OF INVENTION: METHODS OF HUMANIZING ANTIBODY PEPTIDES
; NUMBER OF SEQUENCES: 81
; CORRESPONDENCE ADDRESS:
; ADDRESSEE: MORRISON & FOERSTER
; STREET: 755 Page Mill Road
; CITY: Palo Alto
; STATE: CA
; COUNTRY: USA
; ZIP: 94304-1018
; COMPUTER READABLE FORM:
; MEDIUM TYPE: Floppy disk
; COMPUTER: IBM PC compatible
; OPERATING SYSTEM: PC-DOS/MS-DOS
; SOFTWARE: PatentIn Release #1.0, Version #1.30
; CURRENT APPLICATION DATA:
; APPLICATION NUMBER: US/08/525,539A
; FILING DATE: 14-SEP-1995
; CLASSIFICATION: 424
; ATTORNEY/AGENT INFORMATION:
; NAME: DYLAN, TYLER
; REGISTRATION NUMBER: 37,612
; REFERENCE/DOCKET NUMBER: 27633-20001.21
; TELECOMMUNICATION INFORMATION:
; TELEPHONE: (415) 813-5600
; TELEFAX: (415) 494-0792
; TELEX: 706141
; INFORMATION FOR SEQ ID NO: 17:
; SEQUENCE CHARACTERISTICS:
; LENGTH: 34 amino acids
; TYPE: amino acid
; STRANDEDNESS: single
; TOPOLOGY: linear
US-08-525-539A-17

Query Match 100.0%; Score 52; DB 2; Length 34;
Best Local Similarity 100.0%; Pred. No. 0.038;
Matches 9; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

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Qy          1 FQGSHVPPT 9
              |||||||||
Db         22 FQGSHVPPT 30
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National Library of Medicine - Medical Subject Headings

2006 MeSH

MeSH Supplementary Concept Data

Return to Entry Page

Name of Substance	bortezomib
Record Type	C
Registry Number	0
Entry Term	PS 341
Entry Term	Velcade
Entry Term	PS-341
Entry Term	PS341 cpd
Heading Mapped to	*Boronic Acids
Heading Mapped to	*Pyrazines
Source	Clin Cancer Res 1999 Sep;5(9):2638-45
Pharm. Action	Antineoplastic Agents
Pharm. Action	Protease Inhibitors
Frequency	503
Note	a proteasome inhibitor; structure in first source
Date of Entry	19991117
Revision Date	20030926
Unique ID	C400082

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